Remarks

The Amendments

Claims 10, 12, and 13 have been amended to remove language that was allegedly indefinite. The allegedly indefinite language was placed in new dependant claims 14-16. This is not a narrowing amendment. The amendment merely moves the disputed claim language into dependent claims.

Rejection of Claims 10-13 Under 35 U.S.C. §112, second paragraph

Claims 10-13 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Applicants respectfully traverse the rejection.

The Office Action asserts that the phrase "a mammal, including humans" is indefinite. The claims have been amended to remove the phrase. Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1-6 and 10-13 Under 35 U.S.C. §103(a)

Claims 1-6 and 10-13 stand rejected under 35 U.S.C. §103(a) as allegedly obvious. The Office Action alleges that claims 1-6 and 10-13 are obvious over Bargiotti *et al.* (AA) together with Bargiotti *et al.* (AB), further in view of Eder *et al.*, and Oguro. Applicants respectfully traverse the rejection.

The Office Action asserts that the Bargiotti references teach the compounds of formulas Ia and Ib. The Office Action, however, recognizes that neither reference discloses the administration of compounds of formulas Ia and Ib together with a topoisomerase II inhibitor.

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The Office Action asserts that Eder teaches that etoposide and doxorubicin are topoisomerase II inhibitors that can be used in tumor therapy and that can be advantageously combined with other tumor treatment agents. The Office Action further asserts that Ogura teaches that anthracycline compounds and topoisomerase II inhibitors are among compounds that can be advantageously combined for administration in tumor therapy. The Office Action concludes one of skill in the art would have been motivated to combine topoisomerase II inhibitors with formula Ia and Ib compounds because each of the active ingredients was known in the art for the treatment of tumors or the prevention of metastasis and because Eder and Ogura taught the advantages of combining art-recognized tumor therapies.

Initially, Eder and Ogura do not teach or suggest the combination of topoisomerase II inhibitors with formula Ia and Ib compounds. Eder teaches that etoposide and doxorubicin are **topoisomerase II inhibitors** that can be combined with **topoisomerase I inhibitors**. Eder does not teach or suggest the combination of topoisomerase II inhibitors, such as etoposide and doxorubicin, with any anthracycline derivative at all. Additionally, Ogura teaches the combination of 4-piperidino-piperidine with:

1. topoisomerase II inhibitors;
2. anthracycline antibiotics; and/or
3. other anti-tumor compounds.

Ogura teaches the combination of 4-piperidino-piperidine with anti-tumor compounds and does not teach the combination of compounds that lack 4-piperidino-piperidine.

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Therefore, neither Eder nor Ogura teach the combination of topoisomerase II inhibitors with alkylating anthracyclines of formula Ia or Ib.

Most importantly, the specification provides evidence of a greater than expected result by demonstrating an effect that is greater than the sum of each of the effects taken separately. See, e.g., *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 10 USPQ2d 1843, 1846-47 (Fed. Cir.); MPEP 716.02. That is, the combination of topoisomerase II inhibitors with compounds of formula Ia or Ib provides an unexpected synergistic effect. "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 226 USPQ 1005, 1009 (Fed. Cir. 1985); MPEP 716.02.

In particular, the specification teaches that the combination of 30 mg/kg of etoposide with 1 mg/kg of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl (formula Ia) provides an increase in life span that is more than four times greater than that of each of the compounds when administered individually. Furthermore, there were 4 out of 10 long term survivors among the animals treated with the combination of drugs, while there were 0 out of 10 long term survivors for each of the drugs administered individually. See page 5, first paragraph and Table 1. Additionally, the combination of 13 mg/kg of doxorubicin with 1.5 mg/kg of a compound of formula Ia provides an increase of life span of at least 2.2 times greater than that of each of the compounds administered individually. Furthermore, there were 3 out of 10 long term survivors among the animals treated with the combination of drugs, while there were 0 out of 10

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long term survivors for each of the drugs administered individually. See page 5, second paragraph, and Table 2.

This additive effect is not expected in view of the references cited by the Office Action. First, Eder and Ogura do not teach or suggest the combination of alkylating anthracyclines of formula Ia and Ib with topoisomerase II inhibitors. Second, Eder and Ogura do not teach or suggest that the combination of alkylating anthracyclines of formula Ia and Ib with topoisomerase II inhibitors would provide additive, synergistic results. As such, the synergistic effect of the combination of alkylating anthracyclines of formula Ia and Ib with topoisomerase II inhibitors is unexpected.

Therefore, the combination of Bargiotti *et al.* (AA) together with Bargiotti *et al.* (AB), further in view of Eder *et al.*, and Oguro do not teach or suggest the claimed invention. The combination of references do not teach or suggest the synergistic effect of the combination of alkylating anthracyclines of formulas Ia and Ib with topoisomerase II inhibitors. The combination of references furthermore does not teach or suggest that such an additive effect would be expected in the combination of alkylating anthracyclines of formulas Ia and Ib with topoisomerase II inhibitors. As such, the cited references do not teach or suggest the claimed invention. Applicants respectfully request withdrawal of the rejection.

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Respectfully submitted,

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